



Clinical trial results:

A randomized, single-blinded, multicenter, Phase IV study to compare systemic VEGF protein dynamics following monthly intravitreal injections of 0.5 mg ranibizumab versus 2 mg aflibercept until Week 12 in patients with neovascular (wet) age-related macular degeneration (TIDE AMD)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-001182-27 |
| Trial protocol | DE |
| Global end of trial date | 08 June 2017 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 20 June 2018 |
| First version publication date | 20 June 2018 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CRFB002ADE27 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02257632 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 08 June 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 08 June 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare systemic VEGF-A protein levels following monthly intravitreal injections of 0.5 mg ranibizumab for 3 months vs. monthly intravitreal injections of 2 mg aflibercept for 3 months, as measured by the area under the curve (AUC) from Baseline to Week 12.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 08 April 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Germany: 40 |
| Worldwide total number of subjects | 40 |
| EEA total number of subjects | 40 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 3 |
| From 65 to 84 years | 32 |

| | |
|-------------------|---|
| 85 years and over | 5 |
|-------------------|---|

Subject disposition

Recruitment

Recruitment details:

The study included adult patients with active, newly diagnosed, and untreated wAMD. In total, 41 patients were randomized. One patient was randomized unintentionally and not treated. This patient was not included in any analyses. A total of 40 patients were treated at 6 study sites across Germany. Patients were treated in an outpatient setting.

Pre-assignment

Screening details:

At Screening, the eligibility criteria were performed.

Period 1

| | |
|------------------------------|---------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind ^[1] |
| Roles blinded | Subject, Data analyst, Assessor |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Group 1 |

Arm description:

6 monthly intravitreal injections of 0.5 mg ranibizumab

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ranibizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intraocular use |

Dosage and administration details:

6 monthly intravitreal injections of 0.5 mg ranibizumab

| | |
|------------------|---------|
| Arm title | Group 2 |
|------------------|---------|

Arm description:

3 monthly intravitreal injections of 2 mg aflibercept followed by 3 monthly intravitreal injections of 0.5 mg ranibizumab

| | |
|--|------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Aflibercept |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intraocular use |

Dosage and administration details:

3 monthly intravitreal injections of 2 mg aflibercept followed by 3 monthly intravitreal injections of 0.5 mg ranibizumab

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.

Justification: The study was performed in a single-blinded fashion. Only patients, staff performing BCVA assessments, CRC staff, laboratory staff, and data analysts remained blinded to the identity of the treatment from the time of randomization until database lock.

| Number of subjects in period 1 | Group 1 | Group 2 |
|---------------------------------------|---------|---------|
| Started | 19 | 21 |
| Full Analysis Set (FAS) | 19 | 21 |
| Safety Set (SAF) | 19 | 21 |
| Completed | 18 | 19 |
| Not completed | 1 | 2 |
| Adverse event, non-fatal | 1 | 2 |

Baseline characteristics

Reporting groups

| | |
|---|---------|
| Reporting group title | Group 1 |
| Reporting group description: 6 monthly intravitreal injections of 0.5 mg ranibizumab | |
| Reporting group title | Group 2 |
| Reporting group description: 3 monthly intravitreal injections of 2 mg aflibercept followed by 3 monthly intravitreal injections of 0.5 mg ranibizumab | |

| Reporting group values | Group 1 | Group 2 | Total |
|---|---------|---------|-------|
| Number of subjects | 19 | 21 | 40 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 3 | 3 |
| From 65-84 years | 18 | 14 | 32 |
| 85 years and over | 1 | 4 | 5 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 74.3 | 75.4 | - |
| standard deviation | ± 5.50 | ± 8.94 | - |
| Sex/Gender, Customized Units: Subjects | | | |
| Female | 11 | 10 | 21 |
| Male | 8 | 11 | 19 |
| Race/Ethnicity, Customized Units: Subjects | | | |

End points

End points reporting groups

| | |
|---|---------|
| Reporting group title | Group 1 |
| Reporting group description: 6 monthly intravitreal injections of 0.5 mg ranibizumab | |
| Reporting group title | Group 2 |
| Reporting group description: 3 monthly intravitreal injections of 2 mg aflibercept followed by 3 monthly intravitreal injections of 0.5 mg ranibizumab | |

Primary: Standardized Area Under the Curve (AUC) for VEGF A levels by SIMOA (Quanterix's single molecule array) method for the comparative phase

| | |
|---|---|
| End point title | Standardized Area Under the Curve (AUC) for VEGF A levels by SIMOA (Quanterix's single molecule array) method for the comparative phase |
| End point description: The AUC was calculated using the trapezoidal rule, where all available measurement between Day 1 and Week 12 were used. The AUC was standardized by dividing the calculated value by the number of days from first to last measurement. | |
| End point type | Primary |
| End point timeframe: Baseline up to Week 12 visit (Days 1, 2, 8, 15, 29, 43, 57, 71, 85) | |

| End point values | Group 1 | Group 2 | | |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 | 20 | | |
| Units: pg/mL | | | | |
| arithmetic mean (standard deviation) | 18.78 (\pm 8.460) | 33.95 (\pm 7.659) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | AUC for VEGF A levels for the comparative phase |
| Comparison groups | Group 1 v Group 2 |
| Number of subjects included in analysis | 37 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 ^[1] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -14.98 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -19.64 |
| upper limit | -10.32 |

Notes:

[1] - missing Baseline VEGF-A level covariate values were imputed by the mean value of non-missing Baseline VEGF-A level from all other patients

Secondary: Systemic VEGF-A protein levels from study week 12 to 24

| | |
|-----------------|---|
| End point title | Systemic VEGF-A protein levels from study week 12 to 24 |
|-----------------|---|

End point description:

Systemic VEGF-A protein levels in patients switching from monthly 2 mg aflibercept injections to monthly 0.5 mg ranibizumab compared to patients treated with monthly 0.5 mg ranibizumab from baseline (standardized area under the curve)

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From study week 12 to 24 (Days 85, 99, 113, 127, 141, 155, 169)

| End point values | Group 1 | Group 2 | | |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 | 20 | | |
| Units: pg/mL | | | | |
| arithmetic mean (standard deviation) | 17.93 (\pm 5.316) | 29.07 (\pm 7.863) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | VEGF-A protein levels from study week 12 to 24 |
| Comparison groups | Group 1 v Group 2 |
| Number of subjects included in analysis | 37 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 ^[2] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -11.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15.98 |
| upper limit | -6.94 |

Notes:

[2] - missing Baseline VEGF-A level covariate values were imputed by the mean value of non-missing Baseline VEGF-A level from all the patients with values

Secondary: Systemic VEGF-A levels from study week 12 to 24 (change from baseline)

| | |
|---|--|
| End point title | Systemic VEGF-A levels from study week 12 to 24 (change from baseline) |
| End point description: Adjustment of systemic VEGF-A levels of patients switching from aflibercept to ranibizumab to levels comparable to baseline or to levels comparable as in patients treated from baseline with ranibizumab | |
| End point type | Secondary |
| End point timeframe: From study week 12 to 24 | |

| End point values | Group 1 | Group 2 | | |
|--------------------------------------|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 | 20 | | |
| Units: pg/ml | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change from Baseline at Week 12 | -1.37 (± 5.369) | 23.73 (± 13.700) | | |
| Change from Baseline at Week 14 | -1.00 (± 6.128) | 21.93 (± 15.638) | | |
| Change from Baseline at Week 16 | -0.01 (± 4.675) | 19.26 (± 16.432) | | |
| Change from Baseline at Week 18 | 1.99 (± 5.582) | 11.61 (± 10.844) | | |
| Change from Baseline at Week 20 | 1.62 (± 6.460) | 4.84 (± 11.065) | | |
| Change from Baseline at Week 22 | 0.66 (± 8.109) | 2.45 (± 8.543) | | |
| Change from Baseline at Week 24 | -1.18 (± 3.664) | 0.96 (± 9.553) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Adverse events that occurred in Group 2 are reported in Group 2 irrespective of treatment (Aflibercept, followed by ranibizumab)

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|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

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|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

Reporting groups

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|-----------------------|------------------|
| Reporting group title | Aflibercept 2 mg |
|-----------------------|------------------|

Reporting group description:

Aflibercept 2 mg

| | |
|-----------------------|--------------------|
| Reporting group title | Ranibizumab 0.5 mg |
|-----------------------|--------------------|

Reporting group description:

Ranibizumab 0.5 mg

| Serious adverse events | Aflibercept 2 mg | Ranibizumab 0.5 mg | |
|---|------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 19 (15.79%) | 3 / 21 (14.29%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Benign lung neoplasm | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Optic nerve cupping | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal pigment epithelial tear | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Bone cyst | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 3 %

| Non-serious adverse events | Aflibercept 2 mg | Ranibizumab 0.5 mg | |
|---|------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 16 / 19 (84.21%) | 20 / 21 (95.24%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 2 / 19 (10.53%) | 0 / 21 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Vascular disorders | | | |

| | | | |
|---|---------------------|---------------------|--|
| Hypertension subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 21 (4.76%) 2 | |
| Intermittent claudication subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | |
| Surgical and medical procedures Jaw operation subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | |
| General disorders and administration site conditions Fibrosis subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 21 (4.76%) 1 | |
| Influenza like illness subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 21 (4.76%) 1 | |
| Injection site pain subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 1 / 21 (4.76%) 1 | |
| Sensation of foreign body subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 2 / 21 (9.52%) 2 | |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 21 (4.76%) 2 | |
| Respiratory, thoracic and mediastinal disorders Bronchial wall thickening subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | |
| Nasal congestion subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 21 (4.76%) 1 | |
| Oropharyngeal pain | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 2 / 21 (9.52%) 2 | |
| Pleural effusion subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | |
| Pulmonary embolism subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 21 (4.76%) 1 | |
| Insomnia subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 1 / 21 (4.76%) 1 | |
| Investigations Blood pressure increased subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | |
| Body temperature increased subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 1 / 21 (4.76%) 1 | |
| Electrocardiogram abnormal subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | |
| Haemoglobin E present subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | |
| Intraocular pressure increased subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 2 / 21 (9.52%) 4 | |
| Mean cell haemoglobin concentration increased | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Mean cell haemoglobin increased | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 1 / 21 (4.76%) | |
| occurrences (all) | 1 | 1 | |
| Hand fracture | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Laceration | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac disorders | | | |
| Aortic valve disease | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 0 | 1 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac discomfort | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cardiac fibrillation | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 0 | 1 | |
| Cardiovascular disorder | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Mitral valve incompetence | | | |

| | | | |
|---|----------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 21 (4.76%) 1 | |
| Sinus bradycardia subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | |
| Tricuspid valve incompetence subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 21 (4.76%) 1 | |
| Nervous system disorders Burning sensation subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 21 (4.76%) 1 | |
| Headache subjects affected / exposed occurrences (all) | 2 / 19 (10.53%) 3 | 1 / 21 (4.76%) 1 | |
| Monoparesis subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | |
| Sciatica subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | |
| Eye disorders Anterior chamber cell subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 21 (4.76%) 2 | |
| Blepharitis subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | |
| Choroidal neovascularisation subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 2 / 21 (9.52%) 3 | |
| Conjunctival erosion | | | |

| | | |
|--------------------------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 |
| Conjunctival haemorrhage | | |
| subjects affected / exposed | 4 / 19 (21.05%) | 6 / 21 (28.57%) |
| occurrences (all) | 4 | 9 |
| Conjunctival hyperaemia | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 |
| Corneal erosion | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 1 |
| Dry eye | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 1 / 21 (4.76%) |
| occurrences (all) | 2 | 2 |
| Eye discharge | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 1 |
| Eye pain | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 |
| Eyelid oedema | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 1 |
| Foreign body sensation in eyes | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 3 |
| Lacrimation increased | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 1 / 21 (4.76%) |
| occurrences (all) | 1 | 1 |
| Macular fibrosis | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 |
| Metamorphopsia | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 1 / 21 (4.76%) |
| occurrences (all) | 1 | 2 |
| Ocular discomfort | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 19 (5.26%) | 1 / 21 (4.76%) | |
| occurrences (all) | 1 | 1 | |
| Pinguecula | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Retinal fibrosis | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 2 / 21 (9.52%) | |
| occurrences (all) | 0 | 2 | |
| Retinal scar | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Subretinal fluid | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 0 | 1 | |
| Visual acuity reduced | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 1 / 21 (4.76%) | |
| occurrences (all) | 1 | 2 | |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 1 / 21 (4.76%) | |
| occurrences (all) | 1 | 2 | |
| Vitreous detachment | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 2 / 21 (9.52%) | |
| occurrences (all) | 0 | 2 | |
| Vitreous floaters | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 2 / 21 (9.52%) | |
| occurrences (all) | 2 | 2 | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 0 | 1 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|---------------------|---------------------|--|
| Gastroesophageal reflux disease subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | |
| Nausea subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 21 (4.76%) 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Actinic keratosis subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 21 (4.76%) 1 | |
| Hyperhidrosis subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 21 (4.76%) 1 | |
| Melanosis subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | |
| Photosensitivity reaction subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 2 / 21 (9.52%) 2 | |
| Sebaceous gland disorder subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 21 (4.76%) 1 | |
| Renal and urinary disorders | | | |
| Chronic kidney disease subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | |
| Endocrine disorders | | | |
| Thyroid mass subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 1 / 21 (4.76%) 1 | |
| Back pain | | | |

| | | | |
|--------------------------------|-----------------|----------------|--|
| subjects affected / exposed | 2 / 19 (10.53%) | 0 / 21 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Fibromyalgia | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Neck pain | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 0 | 1 | |
| Spinal column stenosis | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 1 / 21 (4.76%) | |
| occurrences (all) | 1 | 1 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 2 / 21 (9.52%) | |
| occurrences (all) | 1 | 2 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 0 | 1 | |
| Herpes simplex | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hordeolum | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|---|-----------------|-----------------|--|
| Influenza | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 0 | 1 | |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 19 (21.05%) | 4 / 21 (19.05%) | |
| occurrences (all) | 5 | 6 | |
| Metabolism and nutrition disorders | | | |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 0 | 1 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Iron deficiency | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 21 (0.00%) | |
| occurrences (all) | 1 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|---|
| 27 April 2015 | Exclusion criterion no. 4 was changed so that only patients with Type 1 or Type 2 diabetes mellitus with HbA1c > 10% (> 86 mmol/mol) at Screening were excluded from the study. Rationale: a large proportion of wAMD patients who suffered from adult-onset diabetes had the possibility to be included in the study. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported